IMMUNOLOGY AT THE CONFLUENCE OF MULTIDISCIPLINARY APPROACHES

ABSTRACT BOOK

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NOVEL PYRAZOLO[3,4-D]PYRIMIDINE DERIVATIVES SUPRESS P-GLYCOPROTEIN ACTIVITY AND REVERSE MULTIDRUG RESISTANCE IN CANCER CELLS

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P-glycoprotein (P-gp) is an ATP-binding cassette (ABC) transporter whose overexpression in cancer cells is one of the main causes of multidrug resistance (MDR). P-gp overexpression is responsible for reduced intracellular accumulation and efficacy of both targeted therapies and classic chemotherapeutics. Therefore, P-gp has an important role in "absorption, distribution, metabolism, and excretion" – ADME studies. It is also considered as the first cellular defense line and a part of so-called "cellular immunity'. Tyrosine kinase inhibitors (TKIs) have been reported to interact with ABC transporters, and in some cases increase the susceptibility of cancer cells to chemotherapy. We have investigated the anticancer potential of novel tyrosine kinase inhibitors pyrazolo[3,4-d] pyrimidines and their prodrugs against two pairs of sensitive and MDR cancer cell lines with P-gp overexpression: non-small cell lung carcinoma (NCI-H460 and NCI-H460/R) and colorectal carcinoma (DLD1 and DLD1-TxR). The tested compounds displayed significant cell growth inhibition and enhanced the efficacy of doxorubicin and paclitaxel in MDR cancer cells. Some of the TKIs directly interacted with P-gp and inhibited its ATPase activity. A kinetics study showed that the compounds increased the intracellular accumulation of the P-gp substrate rhodamine 123 in a time-dependent manner. Treatment with the compounds did not increase the mRNA expression level of P-gp in resistant cancer cells. The investigated pyrazolo[3,4-d] pyrimidines showed significant potential for reversing P-gp-mediated MDR even in prolonged treatment, making them good candidates for further development regarding treatment of resistant cancers.